POSTER SESSION

1002

Myocardial Infarction: Pathophysiology

Sunday, March 07, 2004, 9:00 a.m.-11:00 a.m.
Morial Convention Center, Hall G
Presentation Hour: 9:00 a.m.-10:00 a.m.

1002-77 Regional Desensitization of β-Adrenergic Receptor Signaling in Swine With Chronic Hibernating Myocardium

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Background: Contractile reserve to submaximal β-adrenergic stimulation is attenuated in patients and swine with hibernating myocardium and the blunted contractile response is not related to metabolic evidence of ischemia. This study tested the hypothesis that there is an attenuation of β-adrenergic signaling arising as a regional adaptive response in hibernating myocardium.
Methods & Results – Pigs (n=8) with chronic hibernating myocardium were studied 3-months after instrumentation with a chronic LAD stenosis. At the time of study, resting subendocardial flow (LAD 0.7±0.2 vs. 1.2±0.1 ml/min/g in normal, p<0.05) and regional LAD wall thickening (LAD 1.9±0.5 vs. 5.5±0.4 mm in normal, p<0.05) were reduced in the absence of infarction. We assessed regional β-adrenergic responsiveness in subendocardial membrane fractions from hibernating LAD vs. normally perfused remote regions. Total β-receptor density was unchanged in hibernating myocardium (LAD: 97 ±13 vs.103 ± 8 fmol/mg in Normal) but there was shift from a 2-state (high and low-affinity) model (Ki: 775 ± 288 pM and 0.9 ± 0.6μM) to a low-affinity β-adrenergic receptor state in hibernating myocardium (Ki: 0.5 ± 0.4μM). The proportion of β1 receptors was unchanged (LAD: 79 ± 1 vs. 75 ±3 % in Normal). Western analysis demonstrated normal levels of adenylyl cyclase and no alterations in G-protein receptor kinase 2 and 5. Interestingly, there were reciprocal changes in Gα-proteins with an increase in Gαi and reduction in Gαs in hibernating myocardium. These changes were associated with reduced isoproterenol and GppNHp stimulated cAMP accumulation while basal and forskolin stimulated responses were unchanged.
Conclusions – These data support the notion that there is a regional attenuation of β-receptor adenylyl cyclase coupling in hibernating myocardium that may lead to attenuated contractile reserve when myocardial viability is present. The observations support the notion that intrinsic adaptations in hibernating myocardium serve to protect the regional circulation from a myocardial supply/demand imbalance when external determinants of myocardial workload increase during sympathetic activation.

1002-78 The Critical Role of Thrombospondin (TSP)-1 in Limiting Expansion of Fibrosis in Healing Myocardial Infarcts: Studies in Dogs and TSP-1 -/- Mice

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Background: Healing of a myocardial infarct depends on suppression of the inflammatory response after scar formation and prevention of its expansion to normal areas. We observed that expression of Thrombospondin (TSP)-1, a potent inhibitor of angiogenesis and activator of TGF-β, is localized in the border zone of healing canine infarcts and hypothesized that it may suppress the inflammatory response, inhibiting local angiogenesis and limiting expansion of fibrotic tissue to the non-infarcted area.
Methods: A canine and a murine model of reperfused myocardial infarction were used. Morphometric variables and gene expression were studied in wild type and TSP-1 -/- mice using immunohistochemistry and RNAse protection assays. In vitro experiments examined the effects of TSP-1 stimulation on canine endothelial cells.
Results: TSP-1 mRNA was induced in canine infarcts after 1 h of ischemia and 3-7 days of reperfusion. TSP-1 protein was localized in the extracellular matrix and microvascular endothelium of the ischemic border zone after 5-28 days of reperfusion. Isolated canine venous endothelial cells showed constitutive expression of TSP-1 mRNA, which was downregulated by TNF-α and IL-1β but was markedly induced by TGF-β and bFGF. TSP-1- stimulated canine endothelial cells demonstrated a significant downregulation of MT1-MMP, but not TIMP-1 or TIMP-2 mRNA expression. Murine infarcts also exhibited marked TSP-1 deposition in the border zone. TSP-1 -/- mice had significantly higher collagen α1(I) mRNA synthesis and increased macrophage and myofibroblast accumulation in the infarct (p<0.05), with extensive infiltration of the neighboring non-infarcted area, when compared with their wildtype littermates (p<0.01). Furthermore, expression of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α was higher in infarcted TSP-1 knockout animals, possibly because of impaired TGF-β activation.
Conclusions: Our findings suggest that TSP-1 expression in the border zone of healing myocardial infarcts may act as a barrier, limiting expansion of the inflammatory process to the non-infarcted myocardium and decreasing inappropriate fibrosis. These effects may regulate post-infarction remodeling.

1002-79 The Peroxisome Proliferator Activated Receptor-α Activator, Fenofibrate, Improves Recovery of Left Ventricular Contractile Function After Ischemia and Reperfusion in Pigs

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Peroxisome proliferator-activated receptor (PPAR)-α is a nuclear receptor involved in substrate metabolism and inflammatory responses. The functional importance of PPAR-α in myocardium is unknown. We determined if chronic treatment with the PPAR-α activator, fenofibrate (FENO), modifies the response to myocardial ischemia (ISC) and reperfusion (REP) in pigs. ***Methods:*** Fifteen pigs were treated with FENO 50 mg/kg/d orally for 4 weeks; 15 untreated pigs served as controls (CON). Plasma FENO concentration was similar to that achieved in clinical use. At 4 wks, both groups underwent 90 min low flow regional myocardial ISC followed by 120 min REP, resulting in myocardial stunning. Regional LV external work (sonomicrometry), blood flow, substrate uptake, and cytokine mRNA expression (IL-1β, IL-6, IF-γ) were measured. ***Results:*** PPAR-α mRNA expression in myocardium was confirmed by ribonuclease protection assay, fulfilling a necessary condition for the action of a PPAR-α activator. Prior to ISC, regional LV function and substrate uptake did not differ between groups. During ISC, reductions in blood flow were similar in both groups. During both ISC and REP, LV function was depressed in both groups but better preserved in FENO than CON (**p<.05, Table**), without differences in myocardial substrate uptake or cytokine mRNA expression. ***Conclusion:*** Chronic treatment with FENO attenuates the severity of LV stunning in pigs. The mechanism of protection appears to be unrelated to substrate uptake or cytokine expression.

Regional LV ext work (fraction of baseline). Note: Baseline function did not differ between groups.

Group	ISC	REP
CON (n=15)	0.30±.03	0.14±.05
FENO (n=15)	0.42±.04	0.26±.05

1002-80 Angiotensin II Inhibition of Vascular Matrix Metalloproteinases in Heart Failure Is Nitric Oxide-Dependent

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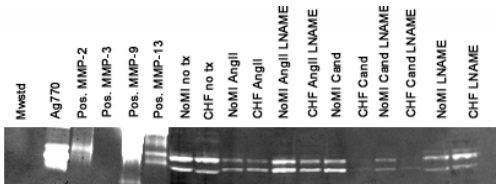
Introduction: The role of angiotensin II (AngII) in promoting vascular remodeling is well established. However, the mechanisms of AngII-mediated remodeling in ischemic heart failure (IHF) are unclear. We hypothesized that AngII mediates vascular remodeling in IHF by modulating the balance of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). **Methods:** Segments of rat aortic segments were treated *ex vivo* with AngII (100 mM) and AT_1 receptor blocker, candesartan (100 mM) for 24 hrs. MMP/TIMP activities were measured using gelatin zymography. In addition, aortic rings were treated with a nitric oxide inhibitor, L-NAME (200 μM) to determine if AngII effects are nitric oxide-dependent.**Results:** In both sham and IHF, AngII decreased MMP-2 and -9 activities compared to untreated controls. L-NAME reversed the effects of AngII on MMP-2 and -9 to 100% in sham and to 80% in IHF, compared to untreated controls. Similarly candesartan reversed the effects of AngII on MMP-2 and -9 to 90% in sham and only to 5% in IHF compared untreated controls. **Conclusion:** AngII-mediated decrease in vascular MMP activities is NO-dependent, while the effects of candesartan on MMP-2 and -9 activation is mainly due to AT_1 receptor blockade. This study suggests that AngII modulation of MMP-2 and -9 may be AT_2 receptor mediated.



1002-81 Age-Related Changes in Adaptation of the Heart to Ischemia-Reperfusion: A Possible Role for NADPH Oxidase-Induced Superoxide Production

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Background: Aging is associated with an increase in myocardial susceptibility to ischemia and a decrease in post-ischemic recovery. However, the mechanisms involved regarding age-related changes are still not clear. The aim of our study was to examine age-related differences in myocardial ischemia-reperfusion and to determine the possible relationship between oxidative stress and age.
Methods: Isolated perfused hearts from young (2 months) (Y), adults (6 months) (A) and old (21 months) (O) rats underwent 30 min of global total ischemia followed by 30 min of reperfusion. The spin-probe CP-H (0.1 μM) was perfused in order to evaluate (in coronary effluents) superoxide-associated oxidative stress during reperfusion using electron spin resonance spectroscopy (ESR). Studies concerning vascular NADPH oxidase were

performed using CP-H associated with ESR, dihydroethidium (DHE) oxidative fluorescence and immunohistochemistry (gp91phox and p22phox).
Results: During the pre-ischemic period, an aged-related decrease in myocardial functional parameters (coronary flow, left ventricular developed pressure, heart rate) was observed. After ischemia, we noted a partial functional recovery which was higher in Y hearts compared with A and O hearts (respectively 17.0±2.2, 5.0±2.8, 5.4±2.6 % of the preischemic values). Our results showed a large release of oxidized CP-H (CP•) during the first minutes of reperfusion which was increased with age (1,296±164 AU in Y hearts, 2,052±188 AU in A hearts, 2,425±405 AU in O hearts). The activity and expression of the vascular NADPH oxidase increased with age according to the ESR approach (14±1 AU in Y group, 20±3 AU in A group, 33±4 AU in O group), fluorescence microscopy (DHE) and immunohistochemistry for gp91phox (0.7±0.1 AU in Y group, 1.5±0.1 AU in A group, 2.1±0.1 AU in O group) and p22 phox; NADPH oxidase involved in these changes being localized in endothelial cells.
Conclusion: Our study suggests that myocardial function and adaptation to ischemia-reperfusion decrease during aging and is related to an higher level of oxidative stress. Endothelial NADPH oxidase appears to be an important contributor to the age-related cardiovascular deterioration.

1002-82 Impact of Body Mass Index on Outcomes After Primary Angioplasty in Acute Myocardial Infarction: The Obesity Paradox

Eugenia Nikolsky, Roxana Mehran, Alexandra J. Lansky, Cindy L. Grines, David A. Cox, Eulogio Garcia, James E. Tcheng, John J. Griffin, Giulio Guagliumi, Thomas Stuckey, Mark Turco, David A. Cohen, Barry Rutherford, Gregg W. Stone, The Cardiovascular Research Foundation, New York, NY

Background The significance of body mass index (BMI) in pts with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PCI) is unknown. Methods and Results. In the CADILLAC trial, 2035 pts undergoing primary PCI for AMI were divided into 3 groups based on BMI: non-obese (<25), mildly obese (≥25 to <30) and very obese (≥30 kg/m^2). Non-obese pts were older, more frequently female, and had higher rate of intervention on LAD, while very obese pts had higher prevalence of diabetes and hyperlipidemia. Target vessel reference diameter was smaller in non-obese (median 2.89 mm) compared to mildly obese (3.01 mm, P<0.0001) and very obese pts (3.05mm, P<0.0001), while number of diseased vessels and ejection fraction did not differ among the groups. The rates of 1-year mortality and of disabling stroke were highest in non-obese pts (Table). However, by multivariate analysis, non-obese pts were not at increased risk of mortality compared with mildly obese (HR=0.68, 95% CI 0.35, 1.32) and severely obese pts (HR=0.55, 95% CI 0.22, 1.34). Rather, predictors of 1-year mortality included age (P=0.0002), LAD infarct vessel (P=0.002), and reduced ejection fraction (P<0.0001). Conclusions. Compared to obese pts, the 1-year prognosis of pts with low-normal BMI is significantly worse after primary PCI for AMI. This apparent "obesity paradox" may be explained by the fact that non-obese pts presenting with AMI are older and more frequently have anterior infarction than their obese counterparts.

Endpoint, %	Body mass index (kg/m^2)			P-value*
	<25.0 N=552	≥25.0 to<30.0 N=915	≥30.0 N=568	
Death	7.5	3.6	1.8	<0.0001
Any MI	1.9	2.4	2.7	0.68
Ischemic TVR	11.4	13.8	14.5	0.27
Disabling stroke	1.4	0.1	0.4	0.006
Any MACE	18.9	17.1	17.0	0.65

*By analysis of variance. TVR=target vessel revascularization. MACE=major adverse cardiac events

1002-83 Prognostic Indications of a Novel Biological Marker of Cardiac Ischemia in Patients Presenting With Chest Pain in an Emergency Setting

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Background: Ischemia Modified Albumin (IMA™) measured by the Albumin Cobalt Binding (ACB®) test (Ischemia Technologies, Denver, CO, USA) is a new quantitative biomarker which measures cobalt binding capacity of albumin modified as a result of myocardial ischemia. This study was conducted to investigate IMA in patients presenting with chest pain and assess its relationship to cardiac outcome at 6 weeks.
Methods: 95 patients (60 ± 17 yrs, 56 males) with chest pain at presentation were studied. Serum samples were collected and traditional cardiac necrosis markers (total CK activity, CKMB, Troponin I (cTnI), Myoglobin) as well as IMA (measured on the KoneLab 20) were determined. Serum for IMA was separated and stored at –20°C prior to analysis. Cut-off values for CK, CKMB, cTnI, Myoglobin and ACB were 180 U/L, 10 U/L, 0.25 µg/L, 110 µg/L and 85 U/mL, respectively.
Results: Time from chest pain onset to presentation was less than 1 hour in 8 patients (8.5%), 1-2 hours in 15 patients (16%), 2-3 hours in 26 patients (27%), 3-6 hours in 13 patients (13.8%), 6-12 hours in 25 patients (26.5%), and >12 hours in 7 patients (7.2%). Myoglobin was elevated in 17 patients (17.8 %), total CK in 24 patients (25.3 %) and cTnI in 14 patients (14.7%) consistent with a high risk population arriving late with respect to pain onset. IMA (100 ± 10 U/mL) was elevated in 84 patients (88%). There was no correlation between IMA and any necrosis marker. When considering adverse cardiac events at 6 weeks (ischemic ECG changes, cTnI increase, MI, revascularisation and death due to cardiac complication), presentation IMA sensitivity was 97.5% (95% CI: 86.8-99.6%), specificity was 17.9% (95% CI: 8.9-30.4%) and NPV was 90.9% (95% CI: 74-100%). IMA was significantly lower in 57 patients with no complications (95 ± 11 U/mL) versus 12 patients with follow-up complications (103 ± 7 U/mL), p < 0.05.

Conclusions: Our results show that IMA is a highly sensitive marker for coronary syndromes even in patients with normal cardiac necrosis marker values, however, it is non-specific. Negative predictive value is high for safe rule-out. IMA could be a useful tool for predicting future cardiac complications in patients with chest pain in the emergency setting.

1002-84 Eplerenone Normalizes Diastolic Relaxation and Extracellular Matrix Accumulation in Aged Rats With Myocardial Infarction

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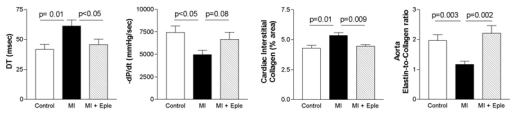
Background: The incidence and severity of CVdiseases increase rapidly with age. Aldosterone blockers have shown benefits in patients with LV dysfunction after MI and in HF. However, efficacy of these agents in experimental models of MI in aged animals has not been explored. **Methods:** 16-month old rats were divided into controls (sham, n= 9), MI (coronary artery ligation, n= 9) and MI with eplerenone in diet (MI + Eple, 120 mg/kg/d, n= 9). Treatment started 18 days after surgery, until sacrifice 3 months later. LV function and dimensions were investigated by echocardiography and hemodynamics. Cardiac fibrosis and the elastin-to-collagen ratio in thoracic aorta were evaluated by histology. **Results:** Untreated MI rats had systolic impairment (LVEF: 58 ± 8 *vs.* 73 ± 2 % in controls, p< 0.05) and clear evidence of diastolic dysfunction (increase of E wave deceleration time DT, and decrease of E wave velocity from 73 ± 3 to 63 ± 5 cm/s (p< 0.05), increase of isovolumic relaxation time from 22 ± 2 to 28 ± 3 ms). LV relaxation was depressed in MI rats (-dP/dt: -33%). Cardiac interstitial fibrosis increased by 23%, while aorta elastin-to-collagen ratio decreased by 40% (Figure). Eplerenone normalized echocardiographic and hemodynamic parameters of diastolic relaxation, cardiac interstitial fibrosis and elastin-to-collagen ratio in aorta (Figure). **Conclusion:** Eplerenone was well tolerated by aged rats. Aldosterone blockade normalized diastolic relaxation after MI, and blunted cardiac and aortic collagen accumulation.



1002-97 Effects of Preinfarction Angina Pectoris on Left Ventricular Function in Diabetic Patients With a First ST-Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention

Calveri Giuseppe, Dajelli Ermolli Carlo, Rogiani Silvia, Saporiti Lucia, Bertelli Ylenia, Caico Salvatore, Uriarte-Salerno Jorge Antonio, Ospedale di Circolo - Università dell'Insubria, Varese, Italy

INTRODUCTION: In patients with acute myocardial infarction undergoing primary percutaneous coronary intervention (PCI) the presence of preinfarction angina (PA), clinical sign of the phenomenon known as "ischemic preconditioning", has been shown to exert in the ischemic myocardium a protective effect on left ventricular function. Whether the same occurs in diabetic patients (DP) remains unknown.
METHODS: We studied 183 nondiabetic patients (NDP) (mean age 67 years, 29% female) and 153 DP (age 69 years, 39% female), hospitalized in our Coronary Care Unit for a first ST-segment elevation acute myocardial infarction and treated with successful PCI on the culprit lesion (TIMI 3 flow restored). 2D-echocardiographic left ventricular ejection function (LVEF) on admission was compared with LVEF at hospital discharge. Time from angina pectoris to balloon (TAB), ST-segment resolution ≥50%, T-wave inversion after PCI, CK-MB peak and in-hospital events were compared in both groups.
RESULTS: In the study population, PA was found in 137 subjects (mean age 67 years, 35% female, 62 DP). When PA was present, creatine kinase peak was sensibly lower in NDP (986 vs 1659 UI/L p=0.025) with earlier ST-segment resolution (9.5 vs 18.3 hours p=0.009) and T-wave inversion (90 minutes after PCI: 62.0% vs 37.3% p=0.007), while no differences were instead observed in diabetic ones (all p=ns). Furthermore, in DP an inverse correlation was evidenced between LVEF after PCI and TAB (R=-0.47 p=0.019) but not in NDP with PA (R=-0.23 p=ns). At discharge, LVEF improvement was superior in NDP (+13.6% vs +8.9% p=ns) especially when PA was present (+21.6% vs 8.1% p=0.041), while in DP with PA no differences were evidenced (+8.5% vs +9.3% p=ns). Similarly, PA was associated to reduced incidence of left ventricular expansion (4.0% vs 14.9% p=0.049) and cardiac failure (12.0% vs 26.9% p=0.035) only in NDP.
CONCLUSIONS: Our results suggest that in diabetic patients with acute myocardial infarction treated with percutaneous coronary intervention, PA do not induce protective effects in the ischemic myocardium, probably due to loss of myocyte preconditioning which reduces tolerance to ischemia and worsens left ventricular function.